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Women are more persistent with monthly bisphosphonate therapy compared to weekly bisphosphonates: 12-month results from 2 retrospective databases

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INTRODUCTION

- Persistence with bisphosphonate (BP) therapy is associated with lower fracture risk in patients with osteoporosis[1]
- Documented long-term persistence with BPs is less than optimal—thereby compromising the full therapeutic benefits of these drugs[2]
- Studies using administrative claims data have confirmed that persistence with weekly BP treatment for osteoporosis is better than with daily therapy[3-4]
- Extended dosing with once-monthly ibandronate corresponds with greater persistence when compared with weekly BPs in 3- and 6-month retrospective longitudinal studies[5-6]
- Claims databases are useful for determining the medication persistence of patients receiving BP therapy
- The advantages of retrospective databases studies over controlled clinical trials include:
  - access to real-world data with clinical practice patients
  - nonintrusive determination of medication-taking behavior
  - large patient populations
  - data collected over long periods of time
- The advantage of using claims databases over retail pharmacy databases is that claims databases allow the investigators to control for more differences in patient baseline characteristics and potential confounders

OBJECTIVE

- To compare persistence in women at least 45 years of age initiating treatment with once-monthly ibandronate or once-weekly BPs (alendronate or risedronate) over a 12-month observation period using data from 2 managed care databases

METHODS

- Deidentified patient data were obtained from 2 large managed care claims databases—provided by i3 Innovus (Eden Prairie, MN) and HealthCore Integrated Research Database (Wilmington, DE)—in parallel studies
- These databases represent over 30 million covered lives
- Persistence was defined as the proportion of patients who remained on therapy with no refill gaps beyond a defined grace period determined by the dosing window for each regimen
  - Ibandronate has a 21-day window after completion of 1 dose before the next dose can be taken, while weekly BPs have a 6-day dosing window—a difference of 15 days
  - To account for this difference, a 30-day gap was used for weekly BP therapy and a 45-day gap (30 + 15-day difference = 45 days) was used for monthly ibandronate in the primary analysis
  - Parallel gap lengths of 30, 45, and 60 days (i3 Innovus) and 30 days (HealthCore) were included as sensitivity analyses to test for consistency across variables

Study supported by Roche and GlaxoSmithKline

- Cox proportional hazards models were used to analyze persistence and to control for potential confounders (including age, patient co-pay, and comorbidities)
- Kaplan-Meier curves were used to determine the median number of days until discontinuation for each group

Study design

- Data collection began with the launch of ibandronate on April 1, 2005 and continued until October 31, 2006 (HealthCore) or November 30, 2006 (i3 Innovus)
- The time of the first-occurring dispensing during the identification period was defined as the index date
- This analysis included a 12-month follow-up observation period from the date of the index prescription
- Data from the 6-month pre-index period were used to group patients based on prior exposure to osteoporosis medication. The classifications were:
  - BP-naïve
  - osteoporosis medication-naïve
  - switched from other BP dosing regimen
- All patients were included in the persistence analysis, irrespective of prior exposure to BPs

Inclusion criteria

- Women at least 45 years of age
- Patients receiving new prescriptions for monthly ibandronate or the weekly formulations of alendronate or risedronate
- Continuous enrollment with both medical and pharmacy benefits for 180 days in the pre-index period and for the 360-day (i3 Innovus) or 365-day (HealthCore) observation period plus the additional days required for each gap employed to determine persistence in the post-index period

Exclusion criteria

- A diagnosis of Paget's disease, drug-induced osteoporosis, malignant or metastatic cancer, human immunodeficiency virus infection (i3 Innovus exclusion) or hyperparathyroidism (HealthCore exclusion) in the 6-month pre-index period
- A prescription for a BP with the same dosing regimen as the index prescription during the pre-index period
  - Patients were permitted to have prior therapy with a different dosing regimen

RESULTS

Patient characteristics

- Patient demographics are shown in **Table 1**

Persistence

- After adjusting for observed factors, monthly users were 25.1% (hazard ratio = 0.749; 95% confidence interval [CI], 0.702–0.796; $P<0.001$) less likely to discontinue therapy vs weekly users in the i3 Innovus analysis (**Table 2**)

Table 1. Patient demographics

	i3 Innovus			HealthCore		
Characteristic	Monthly (n=3512)	Weekly (n=13,967)	*P* value	Monthly (n=1006)	Weekly (n=10,658)	*P* value
Age, y, mean (SD)	59.6 (8.8)	60.0 (9.2)	0.030	59.4 (9.1)	59.4 (9.2)	0.973
DCI, mean (SD)	0.3 (0.66)	0.3 (0.68)	0.892	0.6 (1.0)	0.5 (1.0)	0.020
Mean co-pay, $	31.66	22.69	<0.001	38.70	32.10	<0.001
Pre-index DXA exam, %	41.0	50.9	<0.001	49.0	52.2	0.052
Pre-index fracture, %	2.9	3.3	0.227	4.4	4.7	0.677
OP medication-naïve, %	46.7	84.2	<0.001	60.6	75.5	<0.001
BP-naïve, %	11.1	11.6	ND	24.8	21.5	ND
BP regimen switch, %	42.2	4.2	ND	14.6	3.0	ND

BP, bisphosphonate; DCI, Deyo-Charlson comorbidity index score; DXA, dual-energy X-ray absorptiometry; ND, not determined; OP, osteoporosis; SD, standard deviation.

Table 2. Cox proportional hazards regression for time to discontinuation (primary analyses)

	i3 Innovus			HealthCore		
Variables	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Cohort (monthly vs weekly)	0.749	0.702–0.796	<0.001	0.623	0.575–0.676	<0.001
Age (continuous)	0.993	0.991–0.995	<0.001	0.998	0.995–1.00	0.103
DCI score (continuous)	1.354	1.330–1.379	<0.001	1.072	1.049–1.096	<0.001
Pre-index fracture	1.087	0.988–1.187	0.098	0.906	0.818–1.004	0.060
Pre-index DXA scan	0.668	0.632–0.704	<0.001	0.696	0.667–0.727	<0.001
Average co-pay (continuous)*	1.005	1.003–1.006	<0.001	1.199	1.154–1.246	<0.001
>30 days' supplies	0.636	0.598–0.674	<0.001	0.744	0.727–0.761	<0.001

CI, confidence internal; DCI, Deyo-Charlson comorbidity index; DXA, dual-energy X-ray absorptiometry.
*Average co-pay per day, for HealthCore.

- Monthly users were 37.7% (hazard ratio = 0.623, 95% CI, 0.575–0.676; $P<0.001$) less likely to discontinue therapy vs weekly users in the HealthCore analysis (**Table 2**)
- In the i3 Innovus study, the unadjusted 12-month persistence rates in the primary analysis were significantly higher for patients receiving monthly ibandronate than for patients receiving weekly BPs ($P<0.001$) (**Figure 1**)
- When different gap definitions were used as sensitivity analyses, persistence was still significantly higher for monthly ibandronate compared with weekly BPs ($P<0.001$), with the exception of the analysis using a 30-day gap for both therapies (**Figure 1**)
  - However, due to the differences between weekly and monthly dosing windows, the 30-day gap may not be appropriate for monthly regimens
- In the HealthCore primary analysis, unadjusted 12-month persistence rates were 36.3% for patients receiving monthly ibandronate and 26.9% for patients receiving weekly BPs ($P<0.0001$); for the sensitivity analysis, 28.1% of ibandronate patients were persistent at study end compared to 26.9% of weekly patients ($P<0.001$)
- The median time to discontinuation was 210 days for monthly use and 125 days for weekly use ($P<0.0001$) in the i3 Innovus database primary analysis (**Figure 2**)
- The median time to discontinuation was 205 days for monthly use and 118 days for weekly use ($P<0.0001$) in the HealthCore database primary analysis (**Figure 3**)

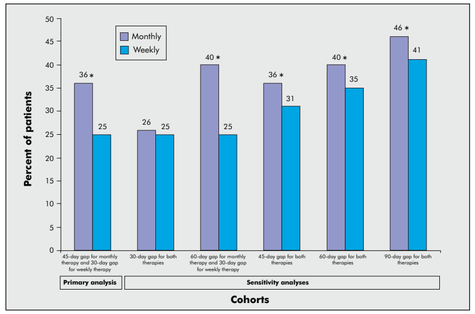

Figure 1. Persistence at 12 months (i3 Innovus database).
The statistical comparison is monthly vs weekly within each gap definition. *$P<0.001$.

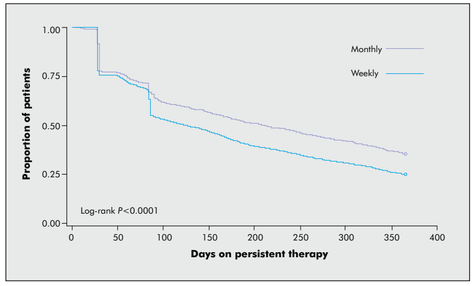

Figure 2. Kaplan-Meier graph of time to discontinuation for patients on weekly or monthly bisphosphonate therapy (i3 Innovus primary analysis)

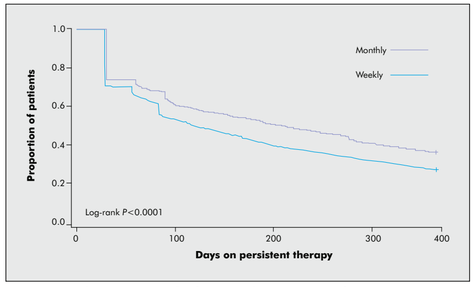

Figure 3. Kaplan-Meier graph of time to discontinuation for patients on weekly or monthly bisphosphonate therapy (HealthCore primary analysis)

- In the i3 Innovus subgroup analysis of patients with no pre-index exposure to BP therapy, the 12-month persistence rate in the primary analysis was higher (32.6% [663 of 2031]) for patients receiving monthly ibandronate than for patients receiving weekly BPs (24.3% [3251 of 13,384]) ($P<0.001$)
  - After adjusting for confounding factors using Cox proportional hazards regression, monthly ibandronate users were 18.7% less likely to discontinue with therapy compared with weekly users (hazard ratio = 0.813; 95% CI, 0.755–0.871; $P<0.001$)

Limitations

- Persistence data acquired during the first 12 months after release of ibandronate may not reflect later usage patterns for monthly ibandronate
  - Study drugs do not have the same formulary status
  - Patient channeling: patients who are intolerant to weekly BPs may switch to monthly treatment
- Discontinuation rates could be affected by differences in filling frequency/patterns
  - Weekly therapy calculations are based on a 28-day month and monthly therapy calculations are based on a 30-day month
- Reviewing refill patterns does not allow for direct observation of actual medication-taking behavior; it is assumed that patients are taking medication as prescribed and following dosing instructions

CONCLUSIONS

- Results from 2 independent managed care databases show that, in a real-world setting, women receiving once-monthly oral ibandronate have significantly greater persistence with therapy at 12 months compared with women receiving weekly oral BPs (alendronate or risedronate)
- Patients receiving monthly ibandronate were more likely to remain on therapy longer than patients receiving weekly BPs, as demonstrated by time-to-discontinuation analyses
- Patients with no pre-index exposure to BPs also had greater persistence with once-monthly ibandronate than weekly BPs
- The increased likelihood of persistence reflects the independent effect of dosing frequency on patient persistence after controlling for potential confounding factors
- The results suggest that patients may be more persistent in the normal clinical setting with monthly ibandronate and are therefore more likely to realize BPs' primary benefit of reduced fracture risk

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